Feasibility and Efficacy of Prehospital Esmolol for Refractory Ventricular Fibrillation

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Research Article

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Abstract

Background: We aimed to assess the feasibility of prehospital bolus dose esmolol for patients with out-of-hospital cardiac arrest (OHCA) and refractory ventricular fibrillation (RVF) treated by a single, high-volume, ground-based emergency medical services (EMS) agency.

Methods: This retrospective observational study evaluated EMS patients with RVF treated from June 10, 2017 to June 10, 2020. Esmolol (0.5mg/kg bolus) was added to the RVF protocol at the mid-point of the study period on December 10, 2018.

Results: We analyzed 61 patients treated with prehospital esmolol and 63 patients treated without esmolol. Median time from EMS arrival to esmolol administration was 17 minutes (interquartile range: 13-22 minutes). Prehospital return of spontaneous circulation (ROSC) was higher in the esmolol group compared to the control group, though statistical significance was not reached (38% versus 24%, p=0.09). Overall, few patients survived to 24 hours (esmolol n=15, pre-esmolol n=16) and fewer survived to hospital discharge (esmolol n=5, pre-esmolol n=5), precluding stable statistical comparisons.

Conclusion: Our findings suggest that esmolol is feasible in the prehospital setting and may lead to increased ROSC. Further large-scale studies are needed to determine the effect of prehospital esmolol for RVF as it relates to survival to hospital discharge.

Trial Registration: This study was approved by the institutional review board at The Baylor College of Medicine and a waiver of informed consent was granted - protocol number H-48383.

Background

Refractory ventricular fibrillation (RVF) is often defined as cardiac arrest with persistent ventricular fibrillation despite initiation of American Heart Association Advanced Cardiac Life Support (ACLS), three defibrillations, three doses of 1mg epinephrine and amiodarone administration (1-2). From a prehospital perspective, this is a specific subset of out-of-hospital cardiac arrest (OHCA), unlike classic electrical storm described in the cardiology literature (3-4), with dismal prognoses and outcomes despite current standard care (5-6). Early defibrillation is known to increase survival in patients with OHCA who present with initial shockable rhythms (7-8), amiodarone potentially increases survival to hospital admission (9), but no pharmacologic treatments have prospectively demonstrated increases in survival with neurologically intact outcomes (10). However, two small hospital-based observational studies (11-12) and earlier animal studies (13-15) have suggested increased survival in RVF with the addition of the ultra-short acting beta-blocker, esmolol, to standard ACLS care. RVF is thought to result from adrenergic surge, often secondary to acute coronary occlusion and myocardial ischemia (16), with esmolol providing benefit by selectively blocking beta-1 adrenergic receptors and decreasing myocardial oxygen demands.

RVF is often first encountered outside the emergency department or hospital environment, making esmolol an attractive potential treatment option for paramedic providers. Within the prehospital literature, however, the feasibility of esmolol use in RVF patients has not been evaluated in the EMS environment. In this study, the feasibility of prehospital bolus dose esmolol in OHCA patients progressing to RVF was assessed by paramedics within a single, high-volume, ground-based EMS agency.

Methods

Study Design and Setting

We conducted a retrospective observational analysis of all OHCA patients with refractory ventricular fibrillation/ encountered by a large, suburban, county-based EMS service in Texas between June 10, 2017 and June 10, 2020. This study was approved by the institutional review board at The Baylor College of Medicine and a waiver of informed consent was granted.

This ground-based EMS agency employs approximately 250 advanced life support providers and more than 1,000 emergency medical technicians (EMTs). In a service area encompassing 1,100 square miles, the agency responds to more than 70,000 annual calls for service.

Prior to December 10, 2018, the treatment protocol for RVF followed standard advanced cardiac life support recommendations including high-quality CPR, epinephrine administration (1mg x 3 doses, Q5min), three defibrillations (200J), anti-arrhythmic administration and advanced airway management with either an endotracheal tube or supraglottic device. The addition of esmolol (0.5mg/kg bolus) to the cardiac arrest treatment protocol for RVF occurred at the midpoint of our data collection period on December 10, 2018. Dual sequential defibrillation (DSD) was available and encouraged, but not required, throughout the entire study period.

The EMS protocol developed for bolus dose esmolol used in this study is noted in Figure 1. Paramedics initially identified RVF and following the third defibrillation, esmolol was available for use after the study midpoint at a dose of 0.5mg/kg. Due to relatively short transport times, we elected to administer only an esmolol bolus without the initiation of a continuous drip.

As part of the update of this protocol at the midpoint of the study, 250 paramedics underwent a mandatory 2-hour training session that included a review of cardiac arrest physiology, focused didactic instruction on the pathophysiology and clinical findings in RVF along with an introduction to specifics of esmolol pharmacology and an introduction to the esmolol treatment protocol (Figure 1). The training sessions occurred approximately one month prior to protocol deployment. This knowledge was then reinforced by a dedicated RVF podcast, produced in-house, which was available and promoted for the duration of the study period. Providers demonstrated an understanding of RVF and the esmolol treatment protocol through both written and psychomotor examinations at the conclusion of the mandatory training session.

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

The prehospital electronic patient care record (ePCR) system was queried for all OHCA patients with three or more defibrillations. EMS patient care records were then individually and independently reviewed by two physician authors (CP and RD) to determine presence of true RVF as defined by shock resistance with persistent ventricular fibrillation, and no degeneration into pulseless electrical activity (PEA) or asystole, during the initial ACLS treatment phase. Cardiac arrests with traumatic etiologies were excluded from the analysis.

Measures

Data elements were abstracted directly from the prehospital ePCR and hospital electronic medical records by a two-person expert review panel consisting of one physician (CP) and one paramedic (BW) using a standardized data collection form. The study variables included patient demographic information, medications, interventions, and cardiac rhythm present throughout the prehospital encounter.

Outcome measures included presence or absence of ROSC during the EMS encounter, 24-hour hospital survival, and survival to hospital discharge. ROSC was ascertained using the prehospital electronic patient care record while survival measures were obtained from the hospital electronic health record.

Statistical Analysis

Descriptive statistics were calculated with frequencies and percentages for categorical variables and continuous variables summarized using medians and interquartile ranges (IQR). Rates of ROSC were compared using Chi-square tests. Multivariable logistic regression modelling was used to assess the association between esmolol and outcome variables while controlling for patient age, sex, and initial rhythm. All analyses were completed using Stata IC Version 15.1 (StataCorp LLC, College Station, TX).

Results

Prior to the addition of esmolol to the EMS protocol, we identified 87 patients with 3 or more defibrillations in the out-of-hospital setting, of which 24 were excluded after full review as RVF was not present. After the addition of esmolol, there were 105 patients with at least 3 defibrillations of which 33 were deemed non-RVF and excluded after review. Two patients with traumatic arrest etiologies were excluded and 9 eligible patients that did not receive esmolol were excluded. The analysis sample consisted of 61 patients treated with esmolol and 63 patients encountered before esmolol was introduced into the EMS protocol (Fig. 2).

Patient and encounter characteristics were similar for patients who did and did not receive esmolol (Table 1). The median age was 67 years in both groups and approximately 28% were female. Bystander CPR was noted in more than 75% of cases. Approximately 87% of patients in both groups presented with an initial rhythm of either VF or VT. Median time to the first dose of epinephrine was 4 minutes in both

groups. The median number of epinephrine doses was slightly higher in the group that did not receive esmolol (5 doses) compared to the group that received esmolol (3 doses). The median EMS scene time was 35 minutes (IQR: 30–41 minutes) in the esmolol group compared to 32 minutes (IQR: 26–41 minutes) in the group that did not receive esmolol.

Table 1
Patient and EMS encounter characteristics.

	Esmolol N = 61	No Esmolol N = 63	p-value
Age, *years*			
Median (IQR)	67 (57–76)	67 (57–77)	0.60
Sex			0.93
Female	27.9% (17)	28.6% (18)	
Male	72.1% (44)	71.4% (45)	
Race			0.56
White	78.7% (48)	85.7% (54)	
Black	4.9% (3)	3.2% (2)	
Hispanic	13.1% (8)	6.4% (4)	
Other/Unknown	3.3% (2)	4.8% (3)	
Bystander CPR			0.91
Yes	77.1% (47)	76.2% (48)	
No	22.9% (14)	23.8% (15)	
Initial rhythm			0.24
VF	83.6% (51)	82.5% (52)	
VT	3.3% (2)	4.8% (3)	
PEA	3.3% (2)	9.5% (6)	
Asystole	9.8% (6)	3.2% (2)	
Dual sequential defibrillation			0.46
Yes	24.6% (15)	19.0% (12)	
No	75.4% (46)	81.0% (51)	
Number of defibrillations			
Median (IQR)	5 (4–7)	6 (5–9)	0.12
Total doses of epinephrine			< 0.01
Median (IQR)	3 (2–4)	5 (4–6)	
Time to first epi, *minutes*			

	Esmolol N = 61	No Esmolol N = 63	p-value
Median (IQR)	4 (3–5)	4 (2–6)	0.79
EMS scene time, *minutes*			
Median (IQR)	35 (30–41)	32 (26–41)	0.21
ED transport			0.01
Yes	62.3% (38)	82.5% (52)	
No	37.7% (23)	17.5% (11)	
EMS transport time, *minutes*			0.51
Median (IQR)	10.5 (8–15)	12 (8.5–17.5)	

Table 2
Prehospital ROSC, 24-hour survival and survival to hospital discharge.

	Esmolol N = 61	No Esmolol N = 63	p-value
Prehospital ROSC			0.09
Yes	37.7% (23)	23.8% (15)	
No	62.3% (38)	76.2% (48)	
24-hour survival			0.92
Yes	24.6% (15)	25.4% (16)	
No	75.4% (46)	74.6% (47)	
Survival to hospital discharge			0.96
Yes	8.2% (5)	7.9% (5)	
No	91.8% (56)	92.1% (58)	

The median on scene arrival time to esmolol administration was 17 minutes (IQR: 13–22 minutes). After esmolol administration 38% (n = 23) of patients achieved prehospital ROSC compared to 24% (n = 15) of patients that did not receive esmolol, though this difference did not reach statistical significance. Survival at 24 hours was similar for those who received esmolol (25%, n = 15) and those who did not receive esmolol (25%, n = 16). In total, 5 patients (8%) from the esmolol group and 5 patients (8%) from the group that did not receive esmolol survived to hospital discharge.

After adjusting for patient age, sex, and initial rhythm, there was a two-fold increase in odds of ROSC during the EMS encounter (OR: 1.99, 95% CI: 0.89–4.47) for patients treated with esmolol compared to patients who were not administered esmolol, though statistical significance was not reached (Fig. 3).

Discussion

In this pragmatic study of patients with RVF encountered by EMS, administering esmolol in the out-of-hospital setting was feasible and non-inferior to standard ACLS treatment. Though no statistical differences were noted, there appeared to be a trend towards higher ROSC for RVF patients administered esmolol. Overall, few patients survived to 24 hours and fewer survived to hospital discharge, making comparisons between groups challenging.

More patients who were administered prehospital esmolol experienced ROSC compared to those treated before the introduction of esmolol into the EMS protocol for RVF. Two in-hospital studies evaluating ED administration of esmolol for patients with OHCA and RVF also identified higher rates of ROSC in the esmolol group (11,12). While ROSC does not directly translate to survival, re-establishing circulation and perfusion in the prehospital setting prior to patient transport may help preserve neurologic function while allowing EMS to safely route the patient to appropriate continued care and advanced interventions. Recently, extracorporeal membrane oxygenation assisted CPR programs have shown benefit for RVF (19), however these programs largely take place in specific, specialized hospital settings. Early ROSC and immediate EMS transport of RVF patients to extracorporeal membrane oxygenation assisted CPR capable facilities may be beneficial within some systems of care where these resources exist.

Overall survival of patients with RVF was low throughout the study period. These findings are consistent with overall poor outcomes observed for patients presenting with RVF (4–6). Prehospital OHCA patients presenting with RVF are a complex, heterogenous patient population with a multi-faceted clinical management pathway. This complexity makes true standardization between patients exceedingly difficult in the EMS setting. For example, while available and encouraged throughout the study period, only ~ 20% of RVF patients in both the pre- and post-esmolol groups received DSD. While the current evidence for the efficacy of DSD in RVF is mixed (17,18), it is possible that increased DSD use in conjunction with esmolol administration could potentially lead to improved outcomes. Also, due to having relatively short EMS transport times and to minimize logistical complexities, we elected to defer initiation of an esmolol drip within our protocol. Two hospital-based studies suggesting improved outcomes with esmolol in OHCA with RVF (11,12) used a 0.5mg/kg loading dose bolus followed by a 0-100mcg/kg/min infusion. Future large-scale prospective EMS investigations of both the pairing of DSD with esmolol in addition to a protocolized initiation of an esmolol infusion following the initial bolus dose are warranted.

Finally, the role of prehospital administered epinephrine in OHCA for patients with RVF is unclear. Use of epinephrine for OHCA in general has been questioned with the results of the PARAMEDIC-2 trial (20) showing no increase in 30-day neurologically intact survival when using epinephrine in OHCA, as

compared to placebo. Additionally, in consideration of patients with RVF, it is worth noting that fibrillated myocardium has significantly increased oxygen consumption relative to normal (21,22), which exogenous epinephrine likely increases via beta adrenergic stimulation. With the underlying pathophysiology of RVF believed to be a result of endogenous catecholamine surge in response to active myocardial ischemia (16), it bears consideration that an early esmolol administration protocol, without exogenous epinephrine, may be beneficial in OHCA, specifically for patients presenting with shockable rhythms and those who progress to RVF. In our study, the time from EMS arrival to esmolol administration was nearly 20 minutes, further evaluation of earlier B-blockade warrants future investigation.

This study was limited by its retrospective nature, small sample size and due to the fact that patients were treated within a single ground-based EMS agency. Further, small sample size and lack of standardization of DSD limited the ability to study the effects of prehospital esmolol on overall RVF morbidity and mortality. Randomized studies with larger sample sizes are needed to further investigate the effects of prehospital esmolol on patient morbidity and mortality in patients with RVF.

Conclusions

This study is the first ground-based EMS prehospital evaluation of the use of esmolol in OHCA patient with RVF. While esmolol use was demonstrated to be feasible in the prehospital setting, under this protocol, there was no change in neurologically intact survival to hospital discharge in RVF patients treated with esmolol as compared to those treated with standard ACLS. Future work must be directed at further prospective, randomized evaluations of a potential role for esmolol in prehospital RVF treatment.

Abbreviations

OHCA – Out of Hospital Cardiac Arrest

RVF – Refractory Ventricular Fibrillation

EMS – Emergency Medical Services

ROSC – Return of Spontaneous Circulation

ACLS – Advanced Cardiac Life Support

EMT – Emergency Medical Technician

DSD – Dual Sequential Defibrillation

ePCR – Electronic Patient Care Record

PEA – Pulseless Electrical Activity

IQR – Interquartile Range

Declarations

Ethics Approval and Consent to Participate

This study was approved by the institutional review board at The Baylor College of Medicine and a waiver of informed consent was granted - protocol number H-48383.

Consent for Publication

Not applicable

Availability of Data and Materials

Deidentified participant data and applicable protocols are available from the corresponding author: cpatrick@mchd-tx.org

Competing Interests

The authors have no competing interests to disclose.

Funding

The authors have no funding sources to disclose.

Author's Contributions

All authors have made substantial contributions to the conception and design of the study (CP, RC,BW,KK,RD), acquisition of data (CP,BW,AM), analysis and interpretation of data (CP, BW, RC), and drafting/revising it critically for important intellectual content (CP,RC).

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Not applicable

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Figures

MCHD	MEDICINE REFERENCE	Esmolol	Page 1 of 1 Last Revision: 02/26/2020

Pharmacologic Class:

- Esmolol is a cardioselective beta1 receptor blocker

Indications:

- Refractory VF/VT, defined as VF/VT that persists after epinephrine x 3, defibrillation x 3, and 300mg of Amiodarone

Contraindications:

- Traumatic Arrest

Dosing:

Adult	Pediatric
▪ 0.5mg/kg Bolus IV/IO	▪ Not Indicated

Pharmacokinetics:

- **Time of Onset**: Rapid onset
- **Duration**: ~9 minutes
- **Half-Life**: Rapid distribution half-life of 2 minutes

Side Effects:

- Hypotension
- Bradycardia

Critical Points:

- Only indicated for the patient in Cardiac Arrest experiencing Refractory Ventricular Fibrillation and/or Refractory Ventricular Tachycardia.
- Consider limiting Epinephrine administration in the RVF patient
- Use in conjunction with Double Sequential Defibrillation

Figure 1

Prehospital esmolol for out-of-hospital cardiac arrest with refractory ventricular fibrillation protocol

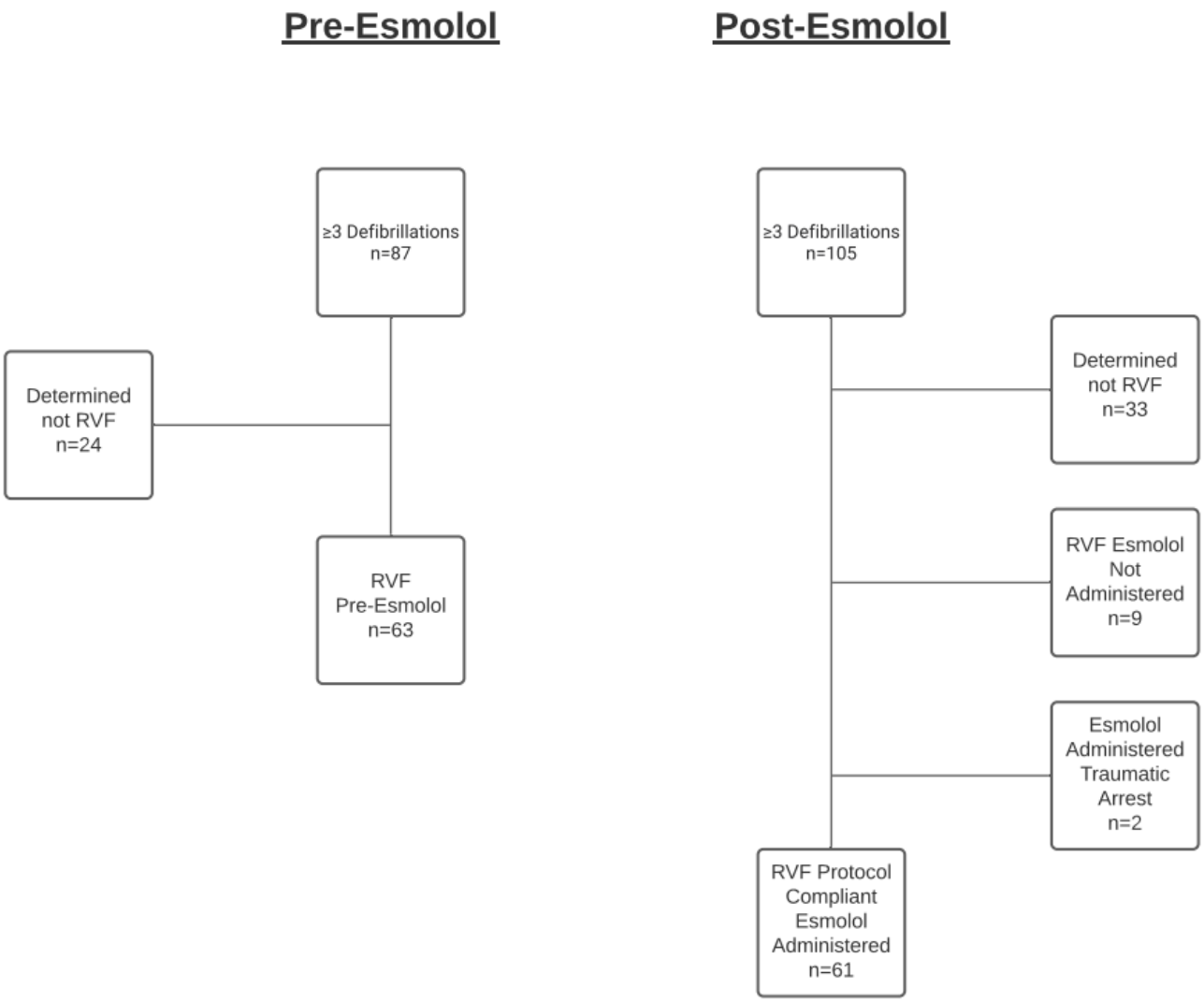

Figure 2

Inclusion of patients in analysis sample

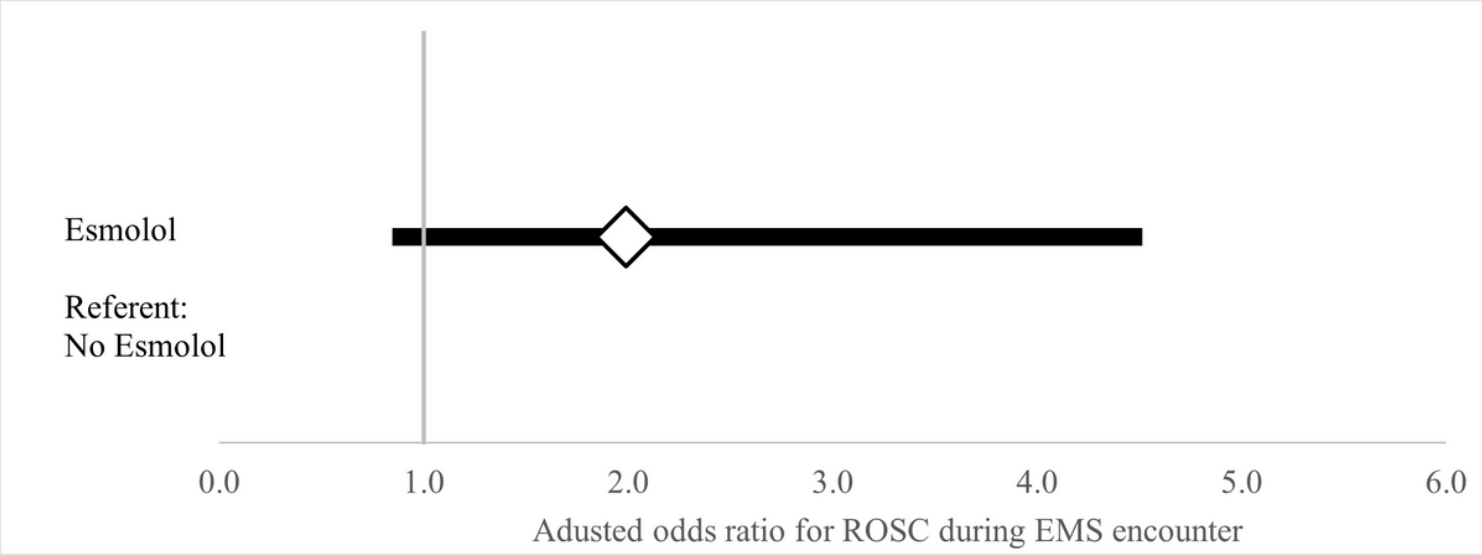

Figure 3

Odds of ROSC during the EMS encounter for patients administered esmolol versus those who did not receive esmolol, adjusted for age, sex, and initial rhythm.